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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/486,069	06/07/95	ENGELHARDT D	ENZ-5(D0)(C2

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EXAMINER	
MARSCHEL,A	

ART UNIT	PAPER NUMBER
1807	24

DATE MAILED: 01/06/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/486,069	Applicant(s) Engelhardt et al.
	Examiner Marschel, Ardin	Group Art Unit 1807

☒ Responsive to communication(s) filed on *3/28/97 and 9/16/97*.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *284-372* is/are pending in the application.

~~Of the above,~~ Claim(s) *1-283 have been canceled.* ~~is/are withdrawn from consideration~~.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *284-372* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

It is noted that a Petition to revive the parent application to the instant application has been granted including the mailing of that decision on 7/9/97.

Applicants' amendments, filed 3/28/97 and 9/16/97, have been entered.

Applicants' arguments and amendments; filed 3/28/97 and 9/16/97; have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. They constitute the complete set presently being applied to the instant application.

If applicant desires priority under 35 U.S.C. § 120 based upon a parent application, specific reference to the parent application must be made in the instant application. It is noted that this appears as the first sentence of the specification following the title. Status of the parent application (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "Patent No." should follow the filing date of the parent application. If a parent application has become abandoned, the expression "abandoned" should follow the filing date of the parent application. It is noted that citation of serial number 06/674,352 and its status has not been included in this first paragraph even though it is in the parentage line.

Claims 284-372 are rejected, as discussed below, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification is such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Consideration of the disclosure as filed has failed to reveal support for newly submitted claims 339-341. It is noted that claims 79-82 and 90 disclosure some specific linkage groups but none of the same scope as newly submitted claims 339-341. The linkages of claims 339-341, 350, 351, 353, 354, 356-358 therefore are NEW MATTER. This rejection is necessitated by amendment.

The optional template dependent or independent limitations of claims 346 and 363 have not been found as filed and are therefore NEW MATTER. This rejection is necessitated by amendment.

The specific localization of modified nucleotides as given in instant claims 365-367 has also not been found as filed and is therefore NEW MATTER. This rejection is necessitated by amendment.

The electrophoretic separating as given in instant claim 368 has also not been found as filed and is therefore NEW MATTER. This rejection is necessitated by amendment.

Consideration of the disclosure as filed has also failed to reveal written description of sequencing gel practice as now given in instant claims 329 and 348 etc. This practice therefore is NEW MATTER. This rejection is necessitated by amendment.

The following rejection is reiterated from the office action, mailed 12/28/95. Applicants argue that the content of

two previous patents should overcome this rejection. In response, the rejection is based on a lack of written description "as filed" in the instant application. The content of other disclosures is moot and non-persuasive in overcoming the rejection because such other disclosures do not support what instant written basis existed as filed. There other disclosures therefore are not directed to the basis of this rejection which is a lack of support for the below summarized limitations "as originally filed". This rejection is repeated as follows and additionally applied to newly added claims that also contain the NEW MATTER limitations as necessitated by amendment. The limitations directed to the covalent attachment of a Sig moiety to a nucleotide base limited to positions other than C^5 of pyrimidines, C^8 of purines, or C^7 of deazapurines as presently given in claim 284 is NEW MATTER. No such negative limitations which are inclusive of numerous other base modification locations are cited in the specification. The presently pending claims dependent from claim 284 also contain this NEW MATTER due to their direct or indirect dependence from claim 284. It is noted that none of these dependent claims are limited so as to not contain said NEW MATTER limitation. Even claims such as 310 contain this limitation in that its Sig attachment limitation only limits the nucleotide (iii) selection but that the claim lacks wording such that this (iii) selection is the only labeled

nucleotide type.

Claims 284-372 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to a scope of covalent attachment sites of the cited "Sig" moiety to bases of nucleic acids wherein said sites are either the N^2 of guanine, the N^6 of adenine, the N^4 of cytosine, or the C^6 of uracil. A thorough review of the disclosure as filed has revealed that the chemistry by which nucleic acid bases may be modified so as to attach a "Sig" moiety only is disclosed for the above four attachment sites within the scope of claims 284 etc. For example, the instant disclosure does not discuss in any way the preparation of N-1 or N-3 modified purines or N-3 or C-2 modified pyrimidines. It is noted that claims 284 etc. are already limited in that certain other, non-base, attachment sites on purines, pyrimidines, and deazapurines are not within the scope of the claims for the at least one modified base in probes used in the claimed methods. It is also noted that certain generalized labeling methods are instantly disclosed such as the formaldehyde coupling of cytochrome C as a bridge between biotin and a nucleic acid molecule on page 58 but that such generalized labeling of a nucleic acid probe lacks both instant disclosure as well as predictability as to where the attachment site is on the probe and therefore fails to predictably form attachments as instantly claimed and thus is deemed to fail to enable the broad

scope of specific base modifications of the instant claims. Ruth is herein cited as summarizing the lack of knowledge at the time of the instant filing regarding the preparation of nucleic acid hybridization probes which contain a signalling moiety. The earliest disclosure of said summary of Ruth is 2/22/83 which is the filing date of the earliest parent thereof and which is also less than a year after the filing date of the instant application. This therefore summarizes the lack of broad hybridization probe preparatory knowledge even after the instant filing date. Ruth summarizes the preparatory knowledge for signal moiety containing labeled probes in column 1, line 43, through column 3, line 45. As cited therein nucleic acid hybridization probes may be prepared either chemically or enzymatically. Enzymatic synthesis using nick translation is discussed wherein certain base modifications have been incorporated into probes but limited in use due to several factors. One of these factors is that only certain modifications may be incorporated by enzymes. Ward et al.(P/N 4,711,955) summarize the factors that were viewed as limitations on modified nucleotides in column 6, line 36, through column 7, line 17, and thereinafter discuss specific base modifications with detailed and lengthy chemical steps. Ruth at column 3, lines 26-45, also summarizes that chemical synthesis has not been disclosed in the prior art as incorporating modified or reporter group containing

nucleotides. Further consideration of Ruth reveals that specific base modifications are therein disclosed such as at column 10, line 57, through column 20 which are accomplished via a lengthy series of detailed reactions including the masking and unmasking of reactive side groups to prevent unwanted modifications. Ruth and Ward et al. are deemed representative of those skilled in the art at about the time of the instant filing date of the instant disclosure. In summary, those skilled in the art at the time of filing of the instant invention viewed the preparation of signal moiety containing nucleic acid probes as lengthy and detailed procedures that were discussed as being accomplished only for certain specific base modifications. It is noted that Ruth or Ward et al. only disclose base modifications at the following sites: C-8 of purines and the C-5 of pyrimidines, N^6 of adenosine, and N^2 of guanosine, and N^4 of cytosine, and C-7 of 7-deazapurines. This documents the lack of enablement of most specific base modifications without detailing lengthy preparatory procedures for those skilled in the art at the time of the instant filing date. Therefore it is deemed undue experimentation to prepare base modified nucleic acid hybridization probes wherein the site of base modifications is other than the N^2 of guanine, the N^6 of adenine, the N^4 of cytosine, or the C-6 of uracil within the scope of instant claims 240 etc. It is again noted that the instant claims are limited

so that base modifications at the C-8 of purines, the C-5 of pyrimidines, and the C-7 of 7-deazapurines are not within their scope. This rejection is reiterated and newly applied as necessitated by amendment due to newly added claims. The rejection has not been argued on its merits other than pointing to issued patents.

Claims 284-372 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to "SM" moieties which are either ribose or deoxyribose. It is noted that claim 284, lines 13-15, cite "PM" attachment points when the nucleotide compound is either a deoxyribonucleotide or ribonucleotide but does not therein limit the "SM" moiety to a sugar moiety that is present in either of these nucleotide types. Thus, the scope of "SM" is only presently limited in claims 284 etc. to being a "sugar moiety" which is much broader in scope than that of ribose or deoxyribose. It is noted that there is no instant discussion as to how to practice the synthesis of nucleotides with "SM" moieties other than that of ribose or deoxyribose. For example, how does someone wishing to utilize glucose as "SM" practice the instant claims? It is noted that in order to broadly practice sugar moieties usage both the synthesis of "PM" attachment is required as well as the "Sig" attachment. Additionally hybridization between the nucleic acid of interest and the oligo- or polynucleotide must still be permitted. No

guidance whatsoever has been instantly set forth directed to accomplishing this broad sugar moiety practice other than that directed to ribose or deoxyribose sugars. It is noted additionally that the numerous examples given in the specification do not include any sugar practice other than ribose or deoxyribose. In the above scope rejection directed to base labeling practice the need for detailed and lengthy procedures to enable the person skilled in the art to prepare nucleotide analogs as well as their incorporation into polymers is summarized. These disclosures include complex chemical protection requirements including those directed to sugar side group protection as well as considerations such as whether enzymes would recognize and incorporate nucleotides into polymers or not as well as other considerations as discussed above. Thus, it is deemed undue experimentation to practice nucleotide compound and polymers containing these compounds without such detailed and lengthy procedural guidance. In summary, such detailed and lengthy guidance is instantly set forth only for "SM" practice directed to ribose or deoxyribose and it is deemed undue experimentation to practice "SM" moieties other than ribose and deoxyribose given the limited instant disclosure. This rejection is reiterated and newly applied as necessitated by amendment due to newly added claims. The rejection has not been argued on its merits other than pointing to issued patents.

Claims 284-372 are rejected, as discussed below, under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 337-372 are vague and indefinite because duplicate and confusing step notations are present. For example, claim 337, lines 4 and 14 both cited step (I). Also, claim 337, third from the last line, confusingly cites step (b) without any corresponding step (a). Claim 348, last line of step (B), cites a (b) without a corresponding (a). Also, this (b) is the second (b) because there is a (b) in line 20. These rejections are necessitated by amendment.

Claim 284, part (b), cites the detection of the presence of "oligo- or polynucleotides which have hybridized to said nucleic acid of interest" but is vague and indefinite when considered in view of part (a) of the claim. Said part (a) cites the practice of "hybridizing..." without any selectivity or specificity directed to preventing hybridization to nucleic acids that are not the "nucleic acid of interest". Thus, such "permitting" practice is reasonably interpreted as inclusive of all levels of stringency including conditions where hybridization is permitted to not only "nucleic acid of interest" but also to other nucleic acids that may be only 90% complementary, 70% complementary, or even only 20% complementary, etc. to the "oligo- or

polynucleotide" cited in part (a). With this broad complementarity practice possible within the scope of part (a), what is meant by applicants' citation of the detecting practice of part (b)? Do applicants mean that selectivity or specificity is to be practiced at the detection step and not at the hybridization step? This suggests that the detecting step is not just a detecting step but is also inclusive of some selection practice. Such a selection practice is not given in step (b) as presently worded. It is noted that the commonly performed practice of a hybridization assay is to control the hybridization step, herein step (a) rather than step (b), so as to be selective as desired. Then the detection step is only directed to the detection of a signal which is then indicative of the presence of the "nucleic acid of interest" in the sample. This, however, is not how claim 284 is presently worded. This unclarity causes even more concern regarding claims such as 324 or 325 which are directed to genetic disorder detection. Additionally there is no mention of the "Sig" moiety in the detection practice of step (b) whereas it is the only "detectable" moiety that is cited in part (a). Do applicants intend that the detection practice of part (b) is inclusive of detection without use of the "Sig" moiety from part (a)? Alternatively, if detection of the "Sig" moiety of part (a) is intended to be the manner of detection of hybridization in part (b), why is part (b) silent regarding said

"Sig" moiety? Clarification is requested as to what applicants mean for the metes and bounds of parts (a) and (b) regarding how the presence of the "nucleic acid of interest" is indicated in the sample versus nucleic acids that are not of interest and what signal is determinative of said presence. Do applicants mean to include some selectivity in either of parts (a) or (b) and, if so, which part or parts? This unclarity is present in all of the instantly depending claims due to their direct or indirect dependence from any of the instant independent claims. This rejection is reiterated and newly applied as necessitated by amendment due to newly added claims.

All of the instant independent claims and those dependent therefrom directly or indirectly all are vague and indefinite because the metes and bounds of the positions on the base at which the Sig moiety is covalently attached is not commensurate with the various disclosures in the specification. See, for example, the directive on page 53, lines 1-4, which limits the modifications as to not interfering with the formation of a double-helix which is not recited in the claims. This rejection is reiterated and newly applied as necessitated by amendment due to newly added claims.

Claims 329-336 and 348-372 are vague and indefinite as to what is meant by "self-signalling", "self-indicating", or "self-detecting" because signals in assays must be received outside of

the reaction moieties in order to record the reaction event. What, therefore, is meant by "self-..." which suggests the signal being turned in unto itself? Clarification is requested. This rejection is necessitated by amendment.

The disclosure is objected to because of the following informalities:

On page 59, line 15, a double dash is present in a chemical formula that is confusing as to what is meant thereby.

Appropriate correction is required.

No claim is allowed.

Applicants' amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

This application is subject to the provisions of Public Law 103-465, effective June 8, 1995. Accordingly, since this application has been pending for at least two years as of June 8, 1995, taking into account any reference to an earlier filed

application under 35 U.S.C. 120, 121 or 365(c), applicant, under 37 CFR 1.129(a), is entitled to have a first submission entered and considered on the merits if, prior to abandonment, the submission and the fee set forth in 37 CFR 1.17(r) are filed prior to the filing of an appeal brief under 37 CFR 1.192. Upon the timely filing of a first submission and the appropriate fee for a large entity under 37 CFR 1.17(r), the finality of the previous Office action will be withdrawn. In view of 35 U.S.C. 132, no amendment considered as a result of payment of the fee set forth in 37 CFR 1.17(r) may introduce new matter into the disclosure of the application.

If applicant has filed multiple proposed amendments which, when entered, would conflict with one another, specific instructions for entry or non-entry of each such amendment should be provided upon payment of any fee under 37 CFR 1.17(r).

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The CM1 Fax Center number is (703) 305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ardin Marschel, Ph.D., whose telephone number is (703) 308-3894. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

December 31, 1997

Ardin H. Marschel

ARDIN H. MARSCHEL
PRIMARY EXAMINER
GROUP 1800